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Intestinal Absorption and Vitamin Levels: Is a New Focus Needed?

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Key Words
Vitamin deficiency · Intestinal absorption · Inflammatory bowel disease

Abstract
Vitamins are micronutrient chemical compounds that cannot be synthesized by an organism but are essential for human metabolism and life. They act as required intermediaries, cofactors or coenzymes in many of the reactions of normal metabolism. In addition, anti-inflammatory effects have been reported for specific vitamins. In inflammatory bowel disease (IBD), vitamin deficiency is often due to malnutrition (due to a decreased food intake) or malabsorption (due to inflamed, malfunctioning mucosa and diarrhea) which results in anemia. Vitamin B_{12} and folic acid supplementation may be necessary in IBD patients, especially those with Crohn's disease (CD) with either inflammation of the terminal ileum or after resection of the terminal ileum. It is also recommended during therapy with sulfasalazine as this compound inhibits the absorption of vitamin B_{12}. Patients with high or continuous inflammatory CD activity and frequent therapy with steroids have an increased risk of low bone mineral density and vitamin D deficiency. These should be monitored regularly and vitamin D should be supplemented. In a recent trial, a trend towards a reduced risk of relapses in CD patients treated with vitamin D was reported. Only limited studies and case reports exist on other vitamin deficiencies, e.g. vitamins A, B_1, B_2, niacine, B_6, C, E and K, found in IBD patients. These are summarized in this review. Regular nutritional monitoring in IBD patients is warranted and requires the special attention of treating physicians and dieticians.

Introduction

Vitamins play a distinct role in human physiology, metabolism and disease. The physiological role is not part of this overview; we concentrate on the role of vitamins in the course of inflammatory bowel disease (IBD) and for associated complications. Deficiencies of single vitamins are rarely endemic, even in developing nations, and are more likely to occur either in the context of general malnutrition or as a result of diseases with malabsorption and/or the need for total parenteral nutrition (TPN). IBD is frequently associated with vitamin deficiencies. The etiology of decreased vitamin levels in IBD is multifactorial and partly due to a pain-related decrease in food intake, e.g. anorexia or else caused by malabsorption i.e. a decreased absorption of vitamins by the inflamed mucosa. Intestinal losses caused by the disease [e.g. blood and hemoglobin during ulcerative colitis (UC)] may also play a role. The most important mechanisms that lead to vitamin deficiencies in IBD are summarized in table 1 [1]. Table 2 summarizes the current literature on the prevalence of vitamin deficiencies among IBD patients and recommended daily allowances [2–14]. As the supplementa-

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Table 1. Pathogenesis of vitamin deficiency in IBD [1]

Reduced food and vitamin intake	anorexia fear of eating from abdominal pain
Active inflammation	mechanisms unknown
Enteric loss of vitamins	exudation from intestinal mucosa interrupted enterohepatic circulation
Malabsorption	loss of absorptive surface from disease, resection or bypass stagnant loop syndrome from strictures fistulae or surgically created blind loops
Miscellaneous	rapid gastrointestinal transit effects of medical therapy effects of parenteral nutrition without supplements

tion of vitamins may significantly improve IBD patients' health status and quality of life, it is important to recognize nutritional deficiencies at an early stage and initiate appropriate treatment. Like this, many patients may experience a further disease aggravation caused by a vitamin deficiency which could otherwise be easily avoided. We consider it unfortunate that somehow the availability of highly effective treatment options has decreased the attention to the issues we discuss here.

Water-Soluble Vitamins

Thiamine (Vitamin B_1)

Thiamine is synthesized by a variety of plants and microorganisms but usually not by animals. Small amounts may be synthesized by microorganisms in the gastrointestinal tract. Thiamine is absorbed both by an active transport process and by passive diffusion. The capacity to absorb the vitamin in the human intestine is about 5 mg/day; approximately 25–30 mg is stored in the body. The recommended daily allowances for thiamine are given in table 2. The vitamin has a widespread distribution in food and is absent only in oils, fats and refined sugar. A substantial loss of the vitamin takes place by heating food over 100°C.

The two major manifestations of thiamine deficiency involve the cardiovascular system (wet beriberi with edema, tachycardia and a high-output state) and the nervous system (dry beriberi with peripheral neuropathy and the Wernicke-Korsakoff syndrome). The patient typically has mixed symptoms involving both the cardiovascular and nervous systems. Wernicke's encephalopathy consists of vomiting, nystagmus (horizontal), ophthalmoplegia, fever, ataxia and progressive mental deterioration and eventually a state of overall confusion. Korsakoff's syndrome consists of retrograde amnesia, an impaired ability to learn and (usually) confabulation. Development of thiamine deficiency occurs mainly in alcoholics and in patients with malabsorption or malnutrition. Several case reports have been published describing vitamin B1 deficiency in patients with Crohn's disease (CD) [15–17]. Hahn et al. [15] describe a CD patient on TPN, in whom beriberi and Wernicke's encephalopathy developed because multivitamin infusions were switched to an oral multivitamin formula. Another case report emphasizes the dependence of thiamine on magnesium and states that if thiamine and magnesium are deficient at the same time, both should be substituted simultaneously [16].

Riboflavin (Vitamin B_2)

Riboflavin participates in a variety of oxidation-reduction reactions. In addition, it is essential to a variety of enzymes such as succinate dehydrogenase and monoamine oxidase. It is either passively absorbed from the gastrointestinal tract as free riboflavin or taken up by an active transport. It is excreted in the urine predominantly in the free form, although a small fraction of the daily turnover is the result of catabolism by microorganisms in the gastrointestinal tract. A deficiency is characterized by a sore throat, hyperemia and edema of the oral mucus membranes, cheilosis, angular stomatitis, glossitis, seborrheic dermatitis and normochromic, normocytic anemia due to red-cell hypoplasia of the bone marrow. No case reports have been published on vitamin B_2 deficiency in IBD patients. Two publications report a decreased vitamin B_2 intake in CD [18, 19] and UC [19].

Niacin (Vitamin B_3)

Niacin is the generic name for nicotinic acid (pyridine-3-carboxylic acid) and derivatives that exhibit the nutritional activity of nicotinic acid. In some sense, niacin is not a 'true' vitamin, since it can be synthesized from the essential amino acid tryptophan. In humans, an average of about 1 mg niacin is formed from 60 mg of dietary tryptophan. Once niacin has been orally ingested, the vitamin is absorbed rapidly from the intestine by both active and passive transport mechanisms. A deficiency in niacin is called pellagra, a chronic wasting disease typically associated with dermatitis, dementia and diarrhea. The dermatitis is bilateral and symmetric, and is present in sites exposed to sunlight (due to photosensitivity).

Table 2. Prevalence of vitamin deficiencies in IBD and recommended daily allowances [2]

	Vitamin	RDA[1]	Frequency in CD, %		Frequency in UC, %		Reference number
			inpatients	outpatients	inpatients	outpatients	
Water-soluble vitamins							
Thiamine	Vitamin B_1	1.5 mg	+[2]	35	n.d.	n.d.	[3]
Riboflavin	Vitamin B_2	1.7 mg	n.d.	n.d.	n.d.	n.d.	–
Niacin	Vitamin B_3	19 mg	n.d.	77	n.d.	n.d.	[3–7]
Pyridoxine	Vitamin B_6	2 mg	n.d.	4.2–37	n.d.	3.8	[3, 8]
Cobalamin	Vitamin B_{12}	2 μg	48	3–35	5	2.9–7.5	[3, 8–11]
Folic acid	Vitamin B_9	200 μg	56–62	10–23	30–41	8.6	[3, 8, 10–13]
Ascorbic acid	Vitamin C	60 mg	+	9.9–84	n.d.	12	[3, 14]
Fat-soluble vitamins							
Retinol	Vitamin A	1,000 μg[a]	11–50	30	93	18–26	[3, 9, 10, 12, 14]
Cholecalciferol	Vitamin D	5 μg[b]	23–75	6–38	35	32	[3, 9, 12]
Tocopherol	Vitamin E	10 mg[c]	0	10–59	40	59	[3, 13]
Menaquinone	Vitamin K	80 μg	+	n.d.	+	n.d.	[2]

n.d. = Not determined. [1] Recommended daily allowances expressed as average daily intakes over time in 25- to 50-year old males. [2] Described, prevalence not reported. [a] Retinol equivalents. [b] As cholecalciferol: 10 μg cholecalciferol = 400 IU of vitamin D. [c] α-Tocopherol equivalents: 1 mg/day α-tocopherol = 1 α-TE.

Mental changes comprise fatigue, insomnia and apathy, which may precede the development of an encephalopathy, characterized by confusion, disorientation, hallucination, loss of memory and eventually organic psychosis. Paresthesias and polyneuritis may be the result of coexisting deficiencies of other vitamins. Diarrhea, when present, results from widespread inflammation of the mucous surfaces. Further symptoms such as glossitis, stomatitis, proctitis, mental depression, abdominal pain, vaginitis, dysphagia and amenorrhea are also described.

Pellagra has seldom been described as a complication of CD. Only 5 case reports are published in the literature [4–7, 20]. The cause of nicotinic acid deficiency in IBD patients may reflect an inadequate intake, malabsorption or increased demand. Suggested treatment regimens are parenteral administration of niacin at 100 mg/day.

Pyridoxine (Vitamin B_6)

Pyridoxine is widely distributed in different kinds of foods: muscle meats, liver, vegetables and whole-grain cereals are among the best sources. More than for most vitamins, the demand is increased in pregnancy. The widespread occurrence of this vitamin in food is probably the reason that isolated pyridoxine deficiency is rare. However, some drugs act as pyridoxine antagonists and may cause a deficiency; among these are isoniazid and penicillamine. The prevalence of vitamin B_6 deficiency in IBD patients was reported to be around 29–30% [8, 14, 21]. Low levels have been associated with hyperhomocysteinemia among IBD subjects [22]; however, the role of a vitamin B_6 deficiency in hyperhomocysteinema etiology remains controversial. Several studies support hyperhomocysteinemia as a risk factor for both arterial and venous thromboembolisms especially in IBD patients [23, 24]. There is a 4-fold increased risk for theomboembolic events in IBD patients, especially in patients with active disease. As outlined above, IBD may be associated with deficiencies in vitamin B_6 and B_{12} that in turn may promote increased homocysteine levels [14, 21, 22]. In contrast, homocysteine levels were found to be normal in the majority of IBD patients, and no elevated homocysteine levels were found in those with low vitamin B_6 serum levels [8]. This questions the role of vitamin B_6 levels regarding the risk of thromboembolism in IBD.

Cobalamin (Vitamin B_{12})

Like most other B vitamins, cobalamin is water-soluble. The only dietary source is animal products such as meat and dairy. During gastric digestion, cobalamin in food is cleaved from its binding protein by acid and pepsin in the stomach and binds to the R factor which is produced in the saliva and the stomach. On entering the duodenum, the cobalamin-R binder complex is digested, releasing the cobalamin, which then binds to intrinsic factor (IF, produced by the parietal cells of the stomach). The cobalamin-IF complex is resistant to proteolytic

digestion and travels to the distal ileum, where specific receptors on the mucosal brush borders bind the cobalamin-IF complex, thereby enabling the vitamin to be absorbed. Once absorbed, cobalamin is bound to transcobalamin II and is then transported to the liver, bone marrow and other cells. Normally, about 2 mg cobalamin is stored in the liver, and another 2–3 mg is stored elsewhere in the body. In view of the minimum daily requirement (1–3 μg/d) and a body store of about 5 mg, it would require about 3–6 years for a normal individual to become deficient in cobalamin if absorption would cease abruptly. Vitamin B_{12} deficiency typically results in ineffective erythropoiesis and megaloblastic anemia as well as sometimes irreversible neurologic and psychiatric abnormalities including personality changes, neuropsychiatric deficits, parasthesias, ataxia and a shuffling gait. Patients with CD may be at a particular risk for vitamin B_{12} deficiency due to ileal inflammation or surgical resection of the ileum leading to impaired absorption of the vitamin [25]. A good review on the prevalence of impaired vitamin B_{12} absorption and deficiency in CD patients has been published by Kulnigg and Gasche [26]. It has been reported that ileal resections <20 cm are not a risk factor for developing a vitamin B_{12} deficiency. For patients with resections of 20–60 cm, a routine monitoring or empirical therapy with vitamin B_{12} is mandatory [27]. An association with gastric CD had also been recognized [28].

Vitamin B_{12} supplementation is often necessary in patients with chronic active CD or resection of the terminal ileum and during therapy with sulfasalazine, which inhibits vitamin B_{12} absorption. Unfortunately, supplementation therapy with vitamin B_{12} and folic acid is only performed in 40% of anemic IBD patients in gastroenterological practices in Switzerland compared to 43% in tertiary referral centers [29]. More than 50% of patients in need of supplementation do not receive the therapy.

Folic Acid (Vitamin B_9)

Folate is synthesized by many different plants and bacteria. Fruits and vegetables constitute the primary source of the vitamin. Some forms of dietary folic acid are labile and may be destroyed by cooking. Folate is absorbed in the duodenum and jejunum and a deficiency may be due to an inadequate diet, malabsorption or drug interactions (e.g. sulfasalazine and methotrexate). Clinical manifestations occur earlier than with vitamin B_{12} deficiency, as folate stores last only 1–2 months. Patients with folic acid deficiency are more apt to be malnourished than those with cobalamin deficiency. The gastrointestinal manifestations of folic acid deficiency consist of diarrhea, cheilosis and glossitis. In contrast to cobalamin deficiency, neurologic symptoms do not occur. The causes of folate deficiencies, especially in IBD patients, are undoubtedly usually multifactorial: anorexia, malabsorption, increased disease activity and drug-induced hemolysis from sulfasalazine are all important mechanisms in CD. It has been proposed that oral folate supplementation should be recommended for patients with IBD as an antineoplastic and antithrombotic agent [30, 31]. Two retrospective publications have identified a folate-induced protective effect against dysplasia and colorectal cancer in patients with UC [30, 31]. Despite these studies which link folate deficiency to an increased risk of cancer in IBD, there are currently no prospective studies providing evidence for a reduced cancer risk in colitis following supplementation.

Ascorbic Acid (Vitamin C)

In most animals, ascorbic acid can be synthesized from glucose. However, humans are unable to synthesize vitamin C and therefore require it in their diet. Vitamin C has a key role as a redox agent for biologic oxidation and is essential in the synthesis of collagen. Many features of vitamin C deficiency (scurvy) result from these defects in collagen synthesis including capillary fragility that underlies the hemorrhagic features, the poor healing of wounds and the bone abnormalities of children. Other features of scurvy include hyperkeratotic papules in which hairs become fragmented and buried, perifollicular hemorrhages and purpura beginning on the backs of the lower extremities coalescing to become ecchymoses, gum involvement that includes swelling, friability, bleeding, loosening of teeth and emotional changes. Normochromic, normocytic anemia is common and is due to bleeding into tissue. The first case of scurvy in CD and a confirmatory low leukocyte ascorbic acid level was reported in 1979 [32]. Gerson and Fabry [33] found that in patients with CD, fistula formation might be related to a local ascorbate deficiency; however, these findings were never confirmed in larger studies. Aghdassi et al. [34] conducted a randomized, controlled study in which patients with CD in remission and proven oxidative stress received vitamin C and vitamin E supplementation or placebo for 1 month. The supplementation significantly decreased all indexes of oxidative stress and increased vitamin C and E plasma concentrations. These results indicate that patients with CD supplemented with antioxidant vitamins E and C reduce their oxidative stress. However, whether there would be any long-term clinical benefit from antioxidant supplementation has still to be determined.

Fat-Soluble Vitamins

Vitamin A

Vitamin A (retinol) can be either directly ingested or synthesized within the body from plant carotenes. The best sources of preformed vitamin A are liver, milk and kidneys, where it occurs largely in the form of fatty acid esters. Retinol is stored as retinyl esters in the liver. The normal body pool is 300–900 mg.

The best-defined function of vitamin A is its role in vision. Deficiencies usually result from inadequate amounts of the vitamin and provitamins in the diet and occur in conjunction with a deficiency of other nutrients. In some developing countries, vitamin A deficiency is a major cause of blindness in the young. In developed countries, a deficiency is usually due to either intestinal malabsorption (as in sprue or after intestinal bypass surgery), abnormal storage (liver disease) or the enhanced destruction or excretion of the vitamin (proteinuria). Typical symptoms of vitamin A deficiency consist of night blindness, dry conjunctiva (xerosis) and ulceration and necrosis of the cornea (keratomalacia). Some case reports described CD patients with low plasma levels of vitamin A [35–37]. During acute flares of IBD, decreased serum vitamin A levels have been found [38]. Serum concentrations of vitamin A do not depend on the localization of disease, previous surgery, duration of IBD or the age and sex of the patients [38]. In IBD patients in remission, normalization of serum retinol levels without substitution of vitamin A has been observed [38].

Newer studies report that vitamin A is an important regulator of the human immune system, especially in the digestive tract. In fact, vitamin A deficiency induces increased blood interferon gamma and chronic diarrhea [39–41]. Vitamin A also has anti-inflammatory properties [42–45]. The cellular effects of vitamin A and its derivatives have been studied in multiple in vitro settings and the molecular effects are well described [46]. Among the effects observed is the inhibition of proinflammatory interleukin (IL)-17-producing Th17 cells and an induction of anti-inflammatory T regulatory cells: When colonic biopsies from patients with UC were cultured and treated with vitamin A derivatives, the upregulation of FOXP3 expression (regulatory, anti-inflammatory T cells) and the downregulation of IL-17 expression was observed [47]. In animal models of colitis treated with vitamin derivatives, lower levels of proinflammatory cytokines (TNF-alpha, IL-1beta and IL-17) and higher levels of regulatory cytokines (IL-10 and TGF-beta) than in untreated mice were detected [47]. Colitis was less severe in the animals treated with vitamin A derivative [42, 47].

These finding suggest that vitamin A might be a new therapeutic target for the treatment of IBD. On the other hand, 2 studies and some case reports have proposed an association of IBD and treatment with vitamin A derivative [48, 49]. This is in contrast to other epidemiological studies that could not find any association of retinoids with the onset of IBD.

Vitamin D

Vitamin D is a hormone rather than a vitamin. Humans get vitamin D from exposure to sunlight, their diet and dietary supplements [50]. With adequate exposure to sunlight, no dietary supplements are needed. Solar ultraviolet B radiation penetrates the skin and converts 7-dehydrocholesterol to vitamin D_3 (cholecalciferol). Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D (calcidiol), which is used to determine a patient's vitamin D status. 25-Hydroxyvitamin D is then metabolized in the kidney to the active form 1,25-dihydroxyvitamin D (calcitriol). This renal production of calcitriol is tightly regulated by levels of plasma parathyroid hormone, serum calcium and phosphorous. The active hormone is then transported through the blood to its target tissue (the small intestine and bone), where it regulates calcium homeostasis [51]. Vitamin D deficiency is found in 22–70% of patients with CD and it has been proposed that it plays an important role in CD pathogenesis [52]. Several lines of evidence support vitamin D as a promising environmental factor that may substantially influence the risk of developing IBD: (1) ecological studies have suggested that the north-south gradient seen in the incidence of IBD patients (with increased incidences of IBD at higher latitudes) might be associated with reduced solar ultraviolet B radiation exposure and consecutive low vitamin D levels [53], (2) studies have linked single-nucleotide polymorphisms in the vitamin D receptor to increased susceptibilities to CD and UC [54, 55], (3) deficiency of 1,25 dihydroxivitamin D and vitamin D receptor knock-out in mice increases the severity of a dextran sulfate sodium colitis, and administration of vitamin D suppresses the expression of several proinflammatory genes [56, 57] and (4) higher predicted plasma levels of 25-hydroxyvitamin D significantly reduce the risk for incident CD in women [58].

Vitamin D appears to have several important actions beyond the maintenance of bone health, including various effects on the immune system [59]. It may play a role in the treatment of IBD-specific complications such as

osteopenia, colorectal neoplasia and depression (for a review see [51]).

To date, only one randomized placebo-controlled trial has been reported assessing the benefits of oral vitamin D_3 treatment in CD patients [60]. In total, 108 CD patients in remission were included in this trial; they were randomized to receive either 1,200 IU vitamin D_3 or placebo once daily for 12 months. The number of relapses during therapy was lower among patients treated with vitamin D_3 and calcium (13%) than among patients treated with calcium alone (29%), but the difference did not reach statistical significance.

Vitamin E

Vitamin E is absorbed from the gastrointestinal tract and enters the circulation via the lymph. The vitamin is stored in all tissues and these tissue stores can protect against vitamin deficiency for long periods. The recommended daily allowance is 10 mg/d (see table 2). The vitamin is widely distributed in food, so a primary deficiency state has never been recognized in otherwise healthy children or adults. Vitamin E deficiency may be associated with a discrete syndrome especially in intestinal fat malabsorption. The manifestations of deficiency include areflexia, gait disturbance, decreased proprioceptive and vibratory sensation and paresis of gaze. To date, no case reports on isolated vitamin E deficiency in IBD have been published. In a cohort of children with IBD, serum levels of vitamin E were within normal values and not significantly different to controls without IBD [61]. These results are different from other studies, where a low intake of or low-serum concentrations of vitamin E in IBD patients were described [14, 21, 62, 63]. As previously described, vitamin E supplementation in patients with IBD significantly decreases all indexes of oxidative stress and increases vitamin E plasma concentrations, indicating the antioxidative properties of this vitamin [34].

Vitamin K

Vitamin K (vitamin K_1) is present in most edible vegetables, particularly in green leaves. Another form of vitamin K (vitamin K_2) is produced by intestinal bacteria but not in sufficient amounts to supply daily requirements. Under ordinary circumstances, about 80% of vitamin K is absorbed from the small bowel into the intestinal lymph. Deficiency can occur in association with diseases that interfere with fat absorption. In addition, long-term treatment with oral antibiotics may temporarily eliminate intestinal bacteria as a source of vitamin K and promote deficiency when the diet is marginal. Vitamin K deficiency leads to low plasma levels of several coagulation factors in the prothrombin complex. Different case reports of CD patients with hemorrhagic problems have been reported in the literature [35, 64, 65]. Malabsorption is probably the most important cause of vitamin K deficiency either from extensive disease or from resection that is severe enough to interfere with bile salt absorption. Recently, an interesting observation was published: a significant correlation of vitamin K deficiency and clinical disease activity was observed in patients with CD [66]. Further prospective studies are required to clarify the role of vitamin K in patients with IBD.

Conclusion

Vitamins play an important role in the metabolism but also in the functions of innate adaptive immunity. The important anti-inflammatory roles of vitamins A, D and E have been described. Vitamin D substitution may play a role in maintenance therapy in IBD. Vitamin deficiencies are frequently observed in patients with IBD. Consequently, these patients should be considered, potentially, as being malnourished. A regular assessment of their vitamin status should be recommended which could lead to specific management, such as suggestions about food choices or vitamin supplementation in severe cases. Diet counselling is important and has proved to be effective in correcting a low nutrient intake in CD patients, and even in improving the course of CD [67, 68].

As we have described for vitamins A and D, vitamins may be used in the future not only for supplementation in the case of deficiencies in IBD patients but also to treat active inflammation or to maintain remission.

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